



(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 1 275 383 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
15.01.2003 Bulletin 2003/03

(51) Int Cl.7: **A61K 31/135, A61K 31/137,**
A61K 9/20

(21) Application number: **02012184.4**

(22) Date of filing: **03.06.2002**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **09.07.2001 IT MI20011457**

(71) Applicant: **Valpharma S.A.
47899 Serravalle (SM)**

(72) Inventors:
• **Valducci, Roberto
47039 Savignano Sul Rubicone (FC) (IT)**
• **Alighieri, Tiziano
47900 Rimini (IT)**
• **Avanessian, Serozh
47900 Rimini (IT)**

(74) Representative: **Negrini, Elena
Agazzani & Associati S.r.l.
Via dell'Angelo Custode 11/6
40141 Bologna (IT)**

(54) **Modified release pharmaceutical composition containing Bupropion HCl as active substance**

(57) Pharmaceutical composition in modified release tablet form containing Bupropion HCl as active substance and including, at the same time, hydrophilic components and hydrophobic ingredients mixed with an excipient substance.

EP 1 275 383 A1

Description**STATE OF THE ART**

5 [0001] Bupropion HCl is a substance having interesting pharmacological characteristics, similar to those of the tricyclic antidepressants.

[0002] Nevertheless Bupropion HCl has an elevated hygroscopicity and susceptibility to the decomposition.

[0003] For this reason various compositions with stabilizing intent have been studied.

10 [0004] For example, the patents n° WO 95/03781 and USP 5,541,231 describe compositions in solid form in which the presence of various acid substances gives stability to Bupropion HCl.

[0005] The patents n° USP 5,427,798 and EP 656775 describe controlled release tablets obtained through the technique of hydrophilic matrixes based on hydroxypropylmethylcellulose.

[0006] However, the stability and the dissolution profile are not satisfactory.

15 [0007] Further modified release compositions are described in the patent n° EP 0171457, which provides for the preparation of a Bupropion HCl core with osmotic components, and then the coating of said core with a membrane insoluble in water but permeable. In such membrane, soluble water substances are suspended, whose solubilization allows to "perforate" the membrane thus enabling the release of Bupropion HCl.

[0008] These techniques have the disadvantage of being very complicated and laborious.

20 SUMMARY

[0009] Now we have found pharmaceutical compositions containing Bupropion HCl as active substance, which allow to overcome the disadvantages of the prior art.

[0010] Such compositions are in tablet form and are characterized by the simultaneous presence of hydrophilic substances and hydrophobic substances.

25 [0011] In particular, the compositions according to this invention include hydroxypropylmethylcellulose, or polyethylene oxide, stearic acid and carnauba wax and an excipient substance like lactose.

[0012] Using the various ingredients in the proper proportions it is possible to modulate the dissolution profile of Bupropion HCl as requested by the European Pharmacopoeia and to obtain tablets suitable for all the commonly utilized dosages.

30 [0013] Furthermore the compositions according to this invention show an elevated reproducibility of the chemical-physical characteristics and the dissolution profile.

DESCRIPTION OF THE INVENTION

35 [0014] The characteristics and the advantages of the pharmaceutical compositions containing Bupropion HCl as active substance according to this invention will be better explained through the following detailed description and through the examples of preparation and characterization.

[0015] Such compositions are prepared in tablet form and include hydrophilic components and hydrophobic components.

40 [0016] A preferred preparation includes, besides Bupropion HCl (BP), hydroxypropylmethylcellulose (HPMC), stearic acid (SA) and carnauba wax (W), as well as an excipient substance like lactose (L). In another preferred preparation hydroxypropylmethylcellulose is replaced by polyethylene oxide.

[0017] For the tablet preparation, the various components in powder form are accurately mixed. The obtained mixture is extruded at a temperature ranging from 45°C to 65°C to obtain a granulate.

45 [0018] The granulate is mixed with lubricating substances commonly utilized in the pharmaceutical technique and then transformed into tablets.

[0019] Each tablet has a Bupropion HCl content ranging from 50 mg to 500 mg.

50 [0020] In the composition preparation according to this invention the various components are used in the following weight proportions:

- BP/(HPMC+SA+W) from 0,5 to 2;
- HPMC / SA / W from 1/1/1 to 1/4/4;
- BP / L from 1 to 2.

55 [0021] As stated above it comes out that the preparation process has the advantage of being realized through more simple operations in comparison with the prior art.

[0022] Furthermore it allows the obtainment of a stable, not hygroscopic, modified release composition, having re-

producible characteristics and suitable for all the commonly used dosages.

[0023] For a better explanation of the invention the following examples are reported.

EXAMPLE 1

[0024] In a Viani granulator, type ST 25, the following ingredients in powder form were mixed:

Bupropion HCl	9.000 g
Hydroxypropylmethylcellulose K 15	1.800 g
Lactose	5.900 g
Stearic Acid	1.800 g
Carnauba Wax	1.800 g

[0025] The obtained mixture was extruded through a Kahl extruder, model press 14-175, with a 0,8 mm net, maintaining the granulation temperature at 50°C. The so obtained granulate was mixed with lubricating substances (magnesium stearate and anhydrous colloidal silica in quantity of 2 and 1 mg per tablet, respectively) and, therefore, compressed into tablets. Each tablet having the average weight of 300 mg had a Bupropion HCl content of 150 mg. The tablets were characterized by the Bupropion HCl release utilizing the method of the European Pharmacopoeia (Paddle apparatus) and the following results were obtained:

Percentage release					
	1 h	2 h	4 h	8 h	12 h
	30	45	67	94	100

[0026] The above indicated tablets were coated and coloured to improve their appearance and protection: such coating leaves the dissolution characteristics unchanged.

EXAMPLE 2

[0027] With the same method described in example n. 1 a granulate with the following composition was prepared:

Bupropion HCl	590 g
Hydroxypropylmethylcellulose K100	96 g
Hydroxypropylmethylcellulose K4	100 g
Lactose	648 g
Stearic Acid	196 g
Carnauba Wax	196 g

[0028] With a portion of the granulate, tablets containing 100 mg of Bupropion HCl were prepared.

[0029] Utilizing the same method of the preceding example the following results could be obtained:

Percentage release					
	1 h	2 h	4 h	8 h	12 h
	34	51	72	96	103

[0030] With the remaining granulate, tablets containing 150 mg of active ingredient were prepared; the so obtained tablets have been coated and coloured. In the in vitro release evaluation the following results were obtained:

Percentage release					
	1 h	2 h	4 h	8 h	12 h
	30	43	62	85	101

EXAMPLE 3

[0031] In a Z double jacket mixer granulator, warmed at 60°C, LLEAL model AM-5, granules with the following composition were prepared:

5

10

Bupropion HCl	300 g
Hydroxypropylmethylcellulose K100	100 g
Lactose	200 g
Stearic Acid	200 g
Carnauba Wax	200 g

15

[0032] The granules were forced through a net with 1000 micrometers aperture size. The so sieved granules were mixed with lubricants and transformed into tablets containing 100 mg of active ingredient: the tablets were analysed obtaining the following results:

20

Percentage release					
1 h	2 h	4 h	8 h	12 h	
33	48	70	84	94	

EXAMPLE 4 (Comparison)

[0033] Example n. 3 was repeated, with the difference that in the preparation of the composition hydroxypropylmethylcellulose was not included and, therefore, the example was carried out without the hydrophilic component.

[0034] The tablets were analysed obtaining the following results:

30

Percentage release							
1 h	2 h	4 h	6 h	8 h	12 h	16 h	20 h
23,0	31,4	42,5	50,4	56,5	65,6	72,1	76,7

[0035] The active ingredient dissolution patterns turned out to be very slow and not capable of being modulated.

35

EXAMPLE 5

40

[0036] Tablets with the same procedure and composition of example n. 3 were prepared, replacing Hydroxypropylmethylcellulose with Polyethylene Oxide having a molecular weight of 1.000.000; the analysed tablets gave the following results:

45

Percentage release				
1 h	2 h	4 h	8 h	
39	62	84	100,5	

EXAMPLE 6

50

[0037] In order to obtain a three layer tablet formulation the following granulates were prepared:

55

6.1 Bupropion HCl was mixed with the excipients in powder, wet with the PVP solution and forced in a net having 1000 micrometers aperture size:

Bupropion HCl	1.000 g
Lactose	400 g
Microcrystalline Cellulose	200 g
PVP at 20% in Ethanol	320 g

The granules were transferred into a desiccator and desiccated for 24 hours at 40°C.

6.2 Utilizing the method described in example n. 3, granules with the following composition were prepared:

5	Bupropion HCl	300 g
	Hydroxypropylmethylcellulose K100	50 g
	Lactose	180 g
	Stearic Acid	180 g
	Carnauba Wax	180 g

10 6.3 Utilizing the method described in example n. 3, granules with the following composition were prepared:

15	Bupropion HCl	300 g
	Hydroxypropylmethylcellulose K100	80 g
	Lactose	150 g
	Stearic Acid	150 g
	Carnauba Wax	180 g

20 [0038] The above described granulates were transformed into three layer tablets by tableting them in the following order:

25	1 st layer utilizing granulate 6.1	26%
	2 nd layer utilizing granulate 6.2	37%
	3 rd layer utilizing granulate 6.3	37%

[0039] Each tablet had an active ingredient content of 100 mg.

[0040] The tablets were analysed after colouring obtaining the following dissolution profile:

30	Percentage release				
	1 h	2 h	4 h	8 h	12 h
	38	55.7	75.4	90	95.5

35 EXAMPLE 7

[0041] Utilizing the granulates previously prepared in example n. 5, two layer tablets containing 150 mg of active ingredient each were prepared.

40 [0042] The two layers had the following composition:

- granulate 6.2 70%
- granulate 6.3 30%

45 [0043] The so obtained tablets were coloured and checked for the in vitro release obtaining the following results:

45	Percentage release				
	1 h	2 h	4 h	8 h	12 h
	21	47	62	85	100

50 **Claims**

55 1. Modified release pharmaceutical composition in tablet form containing Bupropion HCl as active substance, characterized in that, as components, hydroxypropylmethylcellulose, stearic acid and carnauba wax mixed with an excipient substance are included.

2. Composition according to claim 1, wherein such excipient substance is lactose.
3. Composition according to claim 1, wherein such components are present in a weight ratio ranging from 0,5 to 2 of Bupropion HCl and the sum of hydroxypropylmethylcellulose, stearic acid as well as carnauba wax.
- 5 4. Composition according to claim 1, wherein the weight ratio "hydroxypropylmethylcellulose: stearic acid: carnauba wax" is ranging from "1:1:1" to "1:4:4".
- 10 5. Composition according to claim 2, wherein the weight ratio between Bupropion HCl and lactose is ranging from 1 and 2.
6. Composition according to claim 1, wherein the Bupropion HCl content for each tablet is ranging from 50 mg to 500 mg.

15

20

25

30

35

50

55



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 02 01 2184

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	US 6 194 002 B1 (B. C. SHERMAN) 27 February 2001 (2001-02-27) * claims * * example 1 *	1-6	A61K31/135 A61K31/137 A61K9/20
A,D	WO 94 04138 A (WELLCOME FOUNDATION LTD., UK) 3 March 1994 (1994-03-03) * claims *	1-6	
A	US 6 096 341 A (P. SETH) 1 August 2000 (2000-08-01) * claims * * example 6 *	1-6	
A	US 6 238 697 B1 (V. KUMAR ET AL.) 29 May 2001 (2001-05-29) * claims * * column 10, line 8 * * column 10, line 58 * * column 12, line 6 *	1-6	
A	US 4 393 078 A (A. W. PECK) 12 July 1983 (1983-07-12) * claims * * column 1, line 59 *	1-6	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61K
<p>The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	14 October 2002	Scarpioni, U	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

EP 02 01 2184

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

14-10-2002

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 6194002	B1	27-02-2001	NONE		
WO 9404138	A	03-03-1994	AT AU AU CA DE DE EP ES WO GR HK IL JP LU MX NZ SG US ZA	161422 T 677595 B2 4725893 A 2142320 A1 69316015 D1 69316015 T2 0656775 A1 2111168 T3 9404138 A1 3025794 T3 1004323 A1 106693 A 8500110 T 90656 A9 9304967 A1 254947 A 43911 A1 5427798 A 9305942 A	15-01-1998 01-05-1997 15-03-1994 03-03-1994 05-02-1998 16-04-1998 14-06-1995 01-03-1998 03-03-1994 31-03-1998 20-11-1998 10-06-1997 09-01-1996 15-01-2001 31-05-1994 26-04-1996 14-11-1997 27-06-1995 13-02-1995
US 6096341	A	01-08-2000	US	6143327 A	07-11-2000
US 6238697	B1	29-05-2001	NONE		
US 4393078	A	12-07-1983	NONE		

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82